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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Diagnosis and Management of Infective Endocarditis in People Who Inject Drugs

JACC State-of-the-Art Review

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ABSTRACT

The incidence of injection drug use–associated infective endocarditis has been increasing rapidly over the last decade. Patients with drug use–associated infective endocarditis present an increasingly common clinical challenge with poor long-term outcomes and high reinfection and readmission rates. Their care raises issues unique to this population, including antibiotic selection and administration, indications for and ethical issues surrounding surgical intervention, and importantly management of the underlying substance use disorder to minimize the risk of reinfection. Successful treatment of these patients requires a broad understanding of these concerns. A multidisciplinary, collaborative approach providing a holistic approach to treating both the acute infection along with effectively addressing substance use disorder is needed to improve short-term and longer-term outcomes. (J Am Coll Cardiol 2022;79:2037–2057) © 2022 by the American College of Cardiology Foundation.

The global prevalence of injection drug use has been increasing rapidly.[1] In 2017, the U.S. Department of Health and Human Services declared the opioid overdose epidemic a public health emergency. Over the past decade, co-occurring opioid and methamphetamine use disorders have increased significantly.[2] In 2021, the estimated number of U.S. drug overdose deaths exceeded 100,000 individuals over a 12-month period for the first time in history, a 23% increase compared to the previous 12-month period.[3] In addition to drug overdose, infectious complications related to injected drug use, such as drug use–associated infective endocarditis (DUA-IE), have also been rapidly increasing, leading to a sharp increase in the use of acute health care services.[4,5] Data from the Health Care and Utilization Project National Inpatient Sample demonstrate a dramatic increase in the number of DUA-IE hospitalizations (>400% increase from 2005 to 2016)[6] and the proportion of admissions for DUA-IE nearly doubled, from 6.9% to 12.1%, with the marked increase among patients 15-34 years of age (**Figure 1**).[4]

Management of DUA-IE is particularly challenging because of the high long-term morbidity and mortality in a young population, as well as psychosocial and environmental factors contributing to recurrence of substance use and reinfection.[7-10] The decision to proceed with surgical treatment is complicated by the

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SHOUT
SHARE
IT

ABBREVIATIONS AND ACRONYMS

AHA = American Heart Association

DUA-IE = drug use–associated infective endocarditis

ESC = European Society of Cardiology

FDA = U.S. Food and Drug Administration

FDG PET/CT = fluorodeoxyglucose F 18 positron emission tomography/computed tomography

IE = infective endocarditis

MDCTA = multidetector computed tomography angiography

MOUD = medications for opioid use disorder

PMA = percutaneous mechanical aspiration

PWID = persons who inject drugs

SUD = substance use disorder

concerns of reinfection of a prosthetic valve especially in the setting of recurrence of drug use, creating a clinical dilemma for all involved in deciding optimal care for persons with DUA-IE.

Effective treatment of DUA-IE requires addressing the underlying substance use disorder (SUD) as well as psychosocial, environmental, financial, and cultural considerations present in patients' lives. Hence, the complex treatment of these patients, who are often marginalized and vulnerable, demands new paradigms and assembling multidisciplinary teams that ideally include experts in addiction medicine, cardiology, infectious diseases, cardiac surgery, case management, social work, and psychiatry (Figure 2). Multiple institutions are now using multidisciplinary care models incorporating addiction medicine and prediction tools to reduce health care use and improve outcomes.[11-13] In this review, we highlight the unique aspects of caring for persons who inject drugs (PWID) and discuss the state-of-the-art treatment of patients with DUA-IE.

HIGHLIGHTS

- The incidence of DUA-IE is increasing.
- DUA-IE is best managed with a multidisciplinary approach that includes treatment of SUD.
- Studies evaluating optimal treatment are needed to inform clinical practice guideline recommendations on multidisciplinary management to improve clinical outcomes.

EPIDEMIOLOGY, MICROBIOLOGY, AND OUTCOMES OF DUA-IE

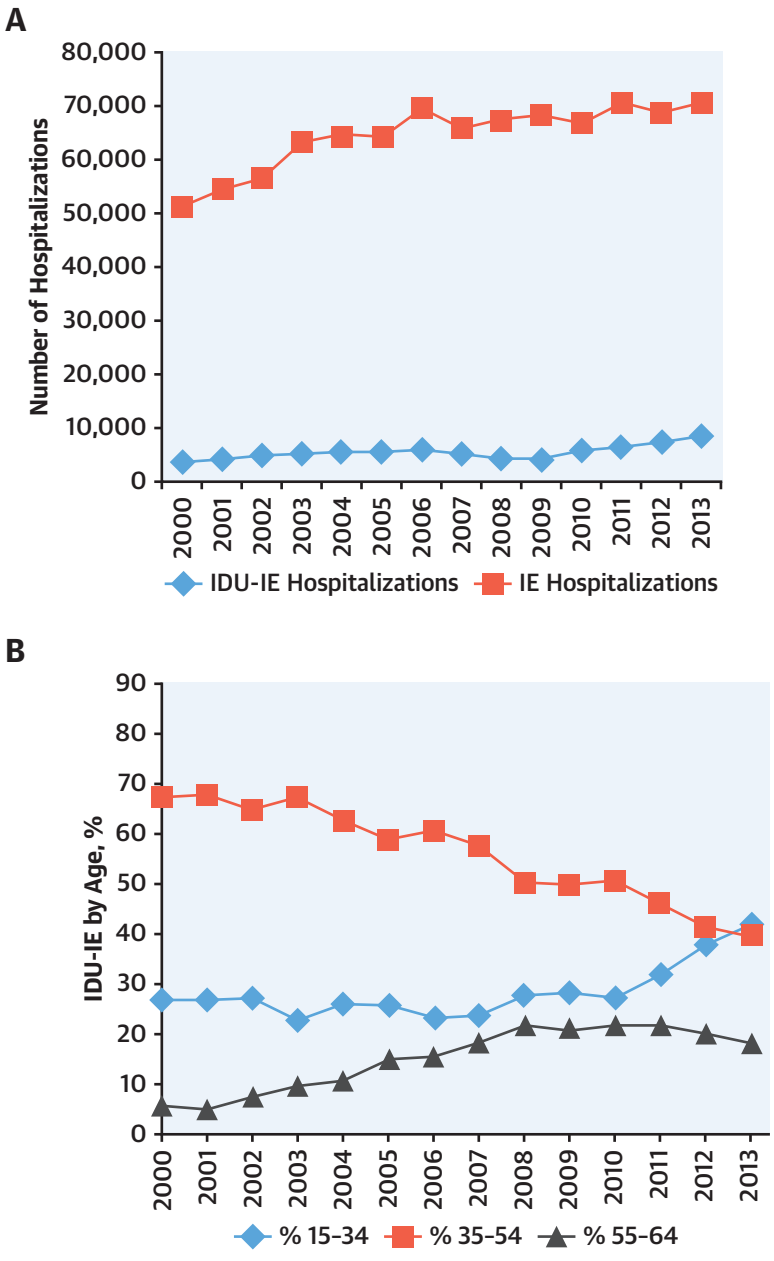
Compared with unselected cohorts with infective endocarditis (IE), individuals with DUA-IE are typically younger, more likely to have had prior endocarditis, and more frequently have comorbid HIV infection and chronic liver disease.[5,7] Patients with DUA-IE also present more frequently with native tricuspid valve endocarditis and concomitant septic pulmonary emboli, are more likely to have *Staphylococcus aureus* infection, and have higher rates of recurrence of infection[14] (Figure 3). Other common organisms that are encountered are listed in Table 1.

However, some investigators suggest that the landscape of DUA-IE is changing. A recent analysis by Pericàs et al[7] that included 2 prospectively collected international cohorts of patients with DUA-IE (ICE [International Collaboration on Endocarditis]) found that >40% had left-sided endocarditis. Data from the National Inpatient Sample also showed a shift in demographics to younger persons with a higher prevalence of women between 2000 and 2013.[4] Cardiac devices, and thus device-related infections, are generally uncommon in this young patient population.

Multiple studies have highlighted a lower mortality rate at index hospitalization in persons with DUA-IE relative to those individuals who do not use drugs, likely because the persons with DUA-IE have a higher incidence of right-sided valve involvement, younger age, and fewer concomitant comorbidities such as renal failure, pre-existing cardiac disease, or heart failure (Figure 4).[8] In cohort studies of DUA-IE, risk factors for in-hospital mortality in right-sided DUA-IE were vegetation size >2 cm or fungal etiology,[15] and risk factors for 6-month mortality in all DUA-IE were prior IE, left-sided IE, polymicrobial etiology, intracardiac complications (paravalvular abscess or fistula), and stroke, whereas cardiac surgery was associated with lower mortality.[7] Unfortunately, lower short-term mortality does not translate into favorable long-term outcomes, most often caused by return to or continued drug use, predilection for recurrent endocarditis, and new sites of infection.[9] A study by Rudasill et al[8] showed that DUA-IE, compared with non-DUA-IE, was associated with lower short-term mortality (6.8% vs 9.6%; $P < 0.001$), but the risk of readmissions caused by subsequent endocarditis, septicemia, and drug use was significantly higher in DUA-IE. In a cohort from the United Kingdom, composed of people experiencing DUA-IE with a median age of 36 years, overall survival was 74%, 63%, 58%, and 44% at 1, 3, 5, and 10 years, respectively (Figure 5), and is significantly lower compared to PWID with other infections ($P = 0.0002$). A total of 47% of patients in this cohort required surgical intervention, and this group unsurprisingly had higher mortality when compared with those who did not require surgery (HR: 1.80; 95% CI: 0.95-3.30). The most common cause of death was relapse or recurrent episode of endocarditis (55%), suggesting adverse outcomes were attributable to ongoing infection.[10]

Furthermore, 90-day readmission after index hospitalization has been reported to be between 22% and 49%, with about one-third of patients using injection drugs again at time of readmission, often leading to

FIGURE 1 **DUA-IE Hospitalizations and Prevalence of DUA-IE by Age Between 2000 and 2013**



The hospitalizations **(A)** for drug use–associated infective endocarditis (DUA-IE) has been increasing with a younger population **(B).** (In the original figure, DUA-IE is indicated as IDU-IE [injection drug use infective endocarditis]). Reproduced with permission from Wurcel et al.[4]

recurrent endocarditis.[8,16] In a small retrospective study by Østerdal et al[17] that analyzed 29 individuals with DUA-IE who underwent surgery for endocarditis, 52% presented with reinfection with a 30-day mortality of 10% after reoperative surgery. They reported that 70% of their patients continued drug use after their first operation as did 44% after their second operation.[17] These findings highlight the need for integrated and comprehensive addiction treatment as well as the unique challenges and conflicts that providers, including a cardiovascular team, often face in caring for patients with DUA-IE.

FIGURE 2 **Multidisciplinary Care for Patients With DUA-IE**

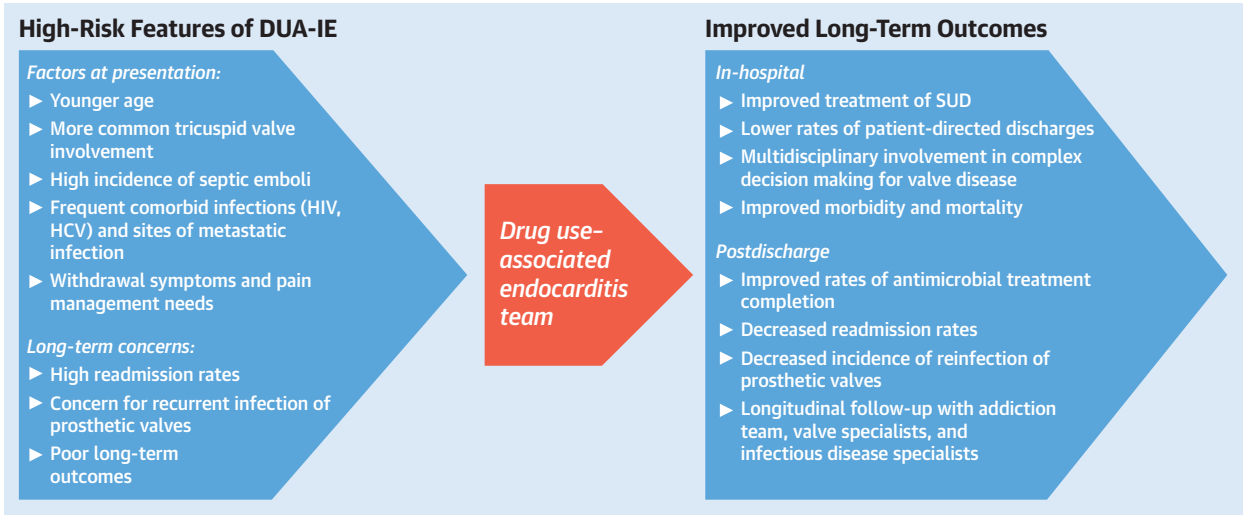
CARDIAC SURGEON
Surgical treatment of IE
ADDICTION MEDICINE SPECIALIST
Adequate treatment of SUD and provide longitudinal support for recovery
INFECTIOUS DISEASE SPECIALIST
Prompt diagnosis & treatment of IE
Provide prevention and screening for comorbid infections
CASE MANAGER
Ensure safe discharge to SUD treatment facility if indicated
SOCIAL WORKER
Provide psychosocial and environmental support
RECOVERY COACH
Provide longitudinal support
CARDIOLOGIST
Prompt assessment of IE and its complications
Provide acute and longitudinal cardiac care
PRIMARY CARE TEAM
Provide care, communicate with patient and family on daily basis
Coordinate care with consulting services
PSYCHIATRIST
Treatment of comorbid mental health disease
INTERVENTIONAL CARDIOLOGIST
PMA for debulking of right-sided vegetations

Team includes specialists in cardiology, cardiac surgery, addiction medicine, infectious disease, social work, psychiatry, case management, recovery coach, and primary team. DUA-IE = drug use–associated infectives endocarditis; IE = infectives endocarditis; PMA = percutaneous mechanical aspiration; SUD = substance use disorder.

DIAGNOSTICS OF DUA-IE

REVIEW OF STANDARD DIAGNOSTICS FOR IE. The modified Duke criteria (Table 2) stratify patients into definite, possible, or rejected cases of IE. The risk that PWID confers for IE is highlighted by the fact that 1 minor Duke criterion, having a history of injection drug use, weighs equally with predisposing heart condition, such as a prosthetic valve or bicuspid aortic valve.[18] One modeling study has shown that the risk of IE relates specifically to injection practices, and persons with high frequency injection (≥1 injection/d) and higher-risk injection techniques (ie, sharing equipment and not using sterile technique) are more likely to develop IE.[19] The differential risk of developing IE based on injection practices makes a strong case for the importance of harm reduction approaches in the setting of ongoing substance use.

FIGURE 3 **Utility of Multidisciplinary Team**


High-Risk Features of DUA-IE
Factors at presentation:
Younger age
More common tricuspid valve involvement
High incidence of septic emboli
Frequent comorbid infections (HIV, HCV) and sites of metastatic infection
Withdrawal symptoms and pain management needs
Long-term concerns:
High readmission rates
Concern for recurrent infection of prosthetic valves
Poor long-term outcomes
Drug use–associated endocarditis team
Improved Long-Term Outcomes
In-hospital
Improved treatment of SUD
Lower rates of patient-directed discharges
Multidisciplinary involvement in complex decision making for valve disease
Improved morbidity and mortality
Postdischarge
Improved rates of antimicrobial treatment completion
Decreased readmission rates
Decreased incidence of reinfection of prosthetic valves
Longitudinal follow-up with addiction team, valve specialists, and infectious disease specialists

High-risk features of patients with DUA-IE and proposed benefits of involvement of a multidisciplinary drug use–associated endocarditis team. HCV = hepatitis C virus; other abbreviations as in Figures 1 and 2.

History and physical examination provide important clues to microbiology, concurrent metastatic infection, and cardiovascular consequences of DUA-IE. Chest radiographs may show pulmonary congestion and/or evidence of chamber dilatation. Transthoracic echocardiography is the standard initial imaging modality for diagnostic evaluation of IE, with guidelines recommending transesophageal echocardiogram for patients who meet Duke clinical criteria for possible IE, those with prosthetic valve(s), and when there is concern for complicated IE.[20] The sensitivity of transthoracic echocardiogram for identifying IE is estimated to be ~70% for native valves and ~50% for prosthetic valves, whereas sensitivity for both native and prosthetic valves improves to ~90% with transesophageal echocardiogram[21] (Table 3). For right-sided endocarditis, which is frequently seen in patients with DUA-IE, transthoracic echocardiogram may be more sensitive given the anterior anatomic location of the tricuspid valve, but vegetations can still be missed with this modality alone.[22] If clinical suspicion remains high for DUA-IE, but transthoracic echocardiogram is unrevealing, transesophageal echocardiogram should be performed and should assess the following: 1) all valves, subvalvular apparatus, and intracardiac hardware to exclude vegetations, abscess formation, intracardiac shunts, or intracardiac fistulae caused by infectious process; and 2) degree of valvular dysfunction. Initial electrocardiogram and continuous electrocardiographic monitoring are also indicated for all patients with IE. Conduction disturbances can occur because of periannular extension of infection, which is predominantly observed in aortic valve endocarditis where prolongation of the PR interval on the electrocardiogram may be the first clue to abscess formation because of the close anatomic proximity of specialized conduction system to the aortic root.

Advanced imaging modalities (Table 3), including those that provide high-quality anatomic information (electrocardiogram-gated multidetector computed tomography angiography [MDCTA] and electrocardiogram-gated cardiac magnetic resonance) as well as high-quality functional data (fluorodeoxyglucose F 18 positron emission tomography/computed tomography [FDG-PET/CT] and leukocyte scintigraphy) have been explored as alternative or adjunctive imaging techniques that can be used as part of the diagnostic evaluation for IE. These imaging techniques may be considered when DUA-IE remains on the differential, but echocardiography has not been confirmatory or results are equivocal.

MDCTA adds diagnostic value for both native and prosthetic valve endocarditis, similar to transesophageal echocardiogram, with improved visualization of perivalvular extension such as abscess and pseudoaneurysm but less accurate for visualization of vegetations than echocardiography is.[23] In a

TABLE 1 Comparative Microbiologic Etiology of DUA-IE and Non-DUA-IE

Pathogen	DUA-IE	Non-DUA-IE		Right-sided Non-DUA-IE
		Worldwide	North America	
Staphylococcus aureus	43-69	28	22-43	70
Viridans group streptococci	5-10	21	9	5-30
Streptococcus bovis	0-1	7	2	5-30
Other streptococci	2	7	6	5-30
Coagulase-negative staphylococci	1-3.7	9	12	
Enterococci	5-8	11	13	2-5
Culture negative	5-6	9	7	
Polymicrobial	3-7	1	1	<1
HACEK	0	2	0.3	
Fungal (candida)	1-5.7	1	1.5-3	<1
Other	2-3	4	4	

Values are %. Data from Goodman-Meza et al,[61] Kadri et al,[102] and Murdoch et al.[103]

DUA-IE = drug use-associated infective endocarditis; HACEK = *Haemophilus aphrophilus, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens*, and *Kingella kingae*.

multivariable analysis adjusted for surgical risk, MDCTA findings of pseudoaneurysm, abscess, and fistula were independently associated with mortality during a mean follow-up of 1.6 ± 1.5 years and when compared to transesophageal echocardiography, MDCTA identified an additional 14% of fistulae, demonstrating its prognostic value in IE.[24] Coronary CT angiography, acquired prospectively can aid in evaluating coronary arteries preoperatively, whereas multiphase imaging through retrospectively gated or wide window electrocardiogram-triggered image acquisition is preferred for evaluation of IE. This allows for reconstruction in any orientation and addition of the fourth dimension of time, which aids in assessment of valve motion and presence of vegetations. MDCTA accordingly has been included in European Society of Cardiology (ESC) modified diagnostic criteria for IE.[25,26]

FDG-PET/CT and leukocyte scintigraphy have also been found to add diagnostic value for prosthetic valve or cardiac device-related infections, and whole-body scans with these modalities along with MDCTA may additionally identify extracardiac sites of infection, such as septic pulmonary emboli.[22,25] While FDG-PET/CT performs poorly for native-valve endocarditis caused by prominent fibrotic reaction and often avascular nature of vegetations, it is effective in detecting infections of prosthetic valves and cardiac implanted electronic devices where there is increased metabolic activity and high inflammatory response on the prosthetic material.[27,28] Furthermore, FDG-PET/CT has been shown to have prognostic value both in prosthetic and native valve endocarditis.[29].

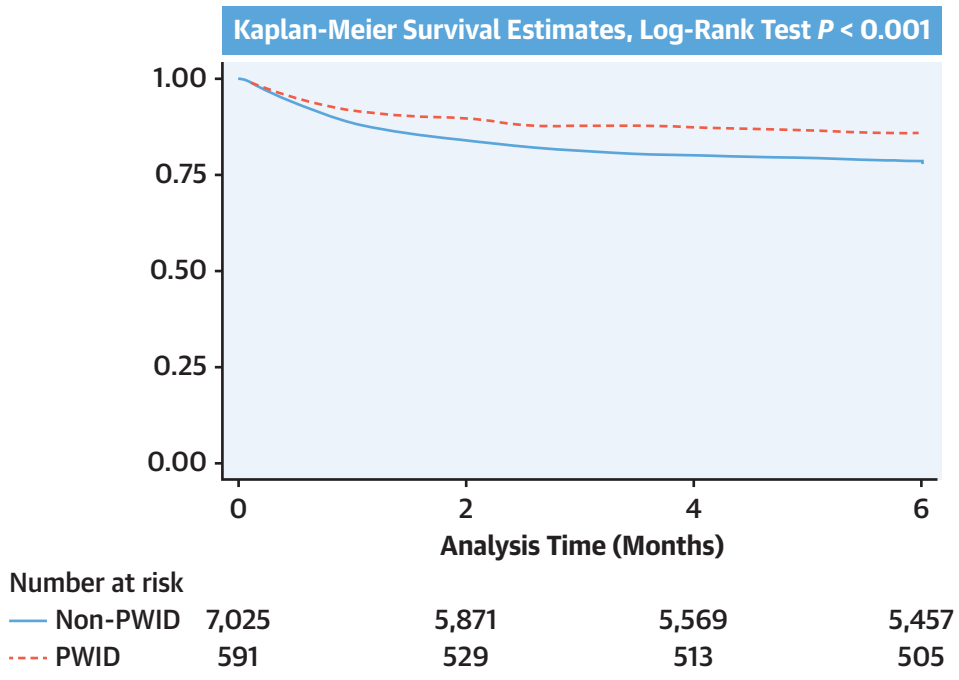
DIAGNOSTIC ASPECTS OF SUBSTANCE USE. Given substantial impact of injectable drug use on risk for IE, the cardiovascular specialist treating patients who are affected should have an understanding of clinical aspects of their SUD.

SUD is a specific diagnosis pertaining to a minority of persons who use drugs and for whom problematic drug use leads to clinically significant impairment or distress impacting health, functioning, and relationships.[30] The hallmark of SUD is the continued use of alcohol or other drugs despite negative consequences. SUD includes a spectrum of illness graded from mild to severe and is diagnosed based on meeting at least 2 of 11 criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.[30] For some individuals, SUD may be mild, episodic, and short-lived and can resolve without formal treatment. However, those with severe SUD can have recurrent symptoms and require long-term evidence-based treatment, similar to the management of other chronic conditions such as hypertension or diabetes.[31] The route of drug use is also relevant when assessing the risk for medical consequences as well as opportunities for harm reduction because injection drug use is associated with a heightened risk for a spectrum of medical and surgical comorbidities as well as serious infectious complications and greater lengths of hospital stay.[32,33]

Addiction consultation services are novel multidisciplinary teams with addiction expertise (composed of addiction medicine/psychiatry physicians, advanced care practitioners, social workers, nurses, and recovery coaches/peer support specialists) that focus on destigmatizing and humanizing addiction while focusing on patient-centered care and harm reduction.[34] This team provides a holistic narrative of patients, including a comprehensive trauma-informed assessment of their addiction and mental health history, identification and diagnosis of SUDs, and assessment of patient's readiness to engage in SUD treatment.[35] There is growing evidence that addiction consultation services and hospital-based SUD care may reduce short-term post-hospitalization substance use and increase abstinence.[36,37]

UNIQUE ISSUES IN DUA-IE DIAGNOSTICS. Relapsed and recurrent infections are more common in patients with DUA-IE and can be particularly difficult to distinguish among PWID.[8] Traditionally, relapsing endocarditis has been defined as a second episode of IE with the same micro-organism within 6 months after the initial episode, whereas recurrent disease is defined by a >6-month separation from initial and subsequent infection. In patients with relapsing IE, a more thorough evaluation for a persistent

FIGURE 4 Kaplan-Meier Survival Curve in Patients With DUA-IE



Observed short-term mortality is better at 6 months among patients who are persons who inject drugs (PWID) with IE compared with in those who are non-PWID with IE. Reproduced with permission from Pericàs et al.[7] Abbreviations as in Figure 1.

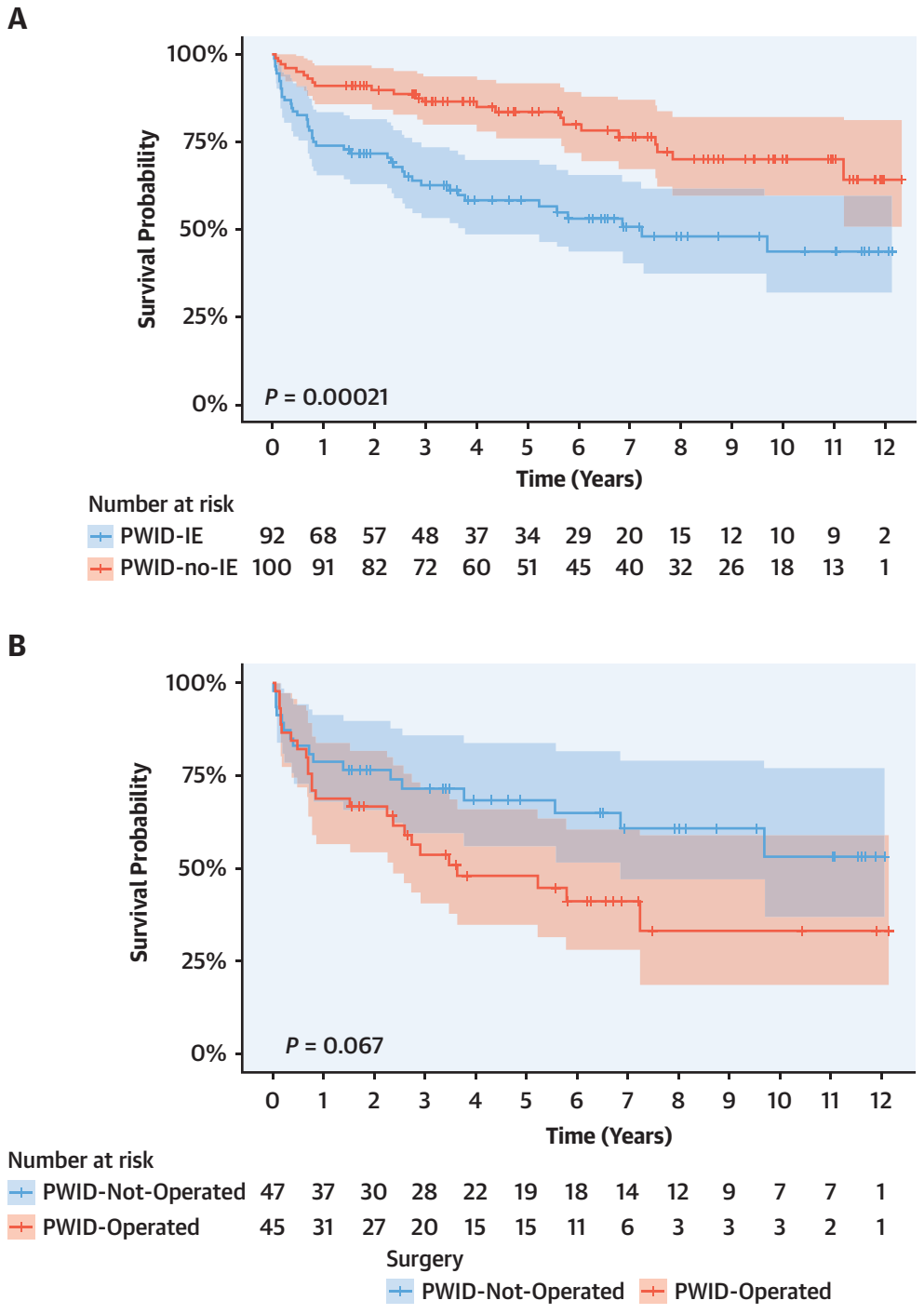
uncontrolled source of infection is required, and prolongation of antimicrobial treatment or surgery may be indicated. However, in PWID, recurrent injection drug use may lead to repeat bacteremia <6 months from last episode of IE, which can complicate the clinician's ability to properly classify repeat episodes of bacteremia and IE as either relapsed or recurrent disease. Molecular techniques for differentiating relapsed from recurrent disease have shown some promise, but availability remains limited.[38] Because of valvular abnormalities that may persist after an acute infection, the American Heart Association (AHA) and ESC recommend an end-of-antimicrobial-therapy transthoracic echocardiogram to establish new baseline valvular morphology following an episode of IE.[20,26] This post-treatment echocardiogram may be valuable in evaluating subsequent episodes of bacteremia. Additional research is needed to better define the role and resource use of transthoracic echocardiogram in this clinical scenario.[39]

METASTATIC INFECTION DIAGNOSIS. Patients with DUA-IE are at risk for other serious bacterial infections related to injection practices, and thus thorough skin and musculoskeletal examinations for infections are required. Once a metastatic site of infection is identified, additional percutaneous or surgical interventions for source control may be required, because persistent foci of infection may lead to relapsing IE. In scenarios where valve surgery for IE is being considered, source control of metastatic sites of infection is of paramount importance because seeding of cardiac hardware may be devastating.

UNIQUE ASPECTS OF CARING FOR PWID

THE NEED FOR MULTIDISCIPLINARY CARE. The substantial risk for morbidity and mortality in persons with DUA-IE, in contrast to their often younger age,[40] requires an innovative framework. Endocarditis teams that use multidisciplinary approaches to specifically optimize and formalize care of patients with DUA-IE have been developed at several institutions[11–13] (Central Illustration). Further studies are urgently needed to pilot interventions and improve outcomes in DUA-IE and to integrate addictions medicine and social work principles into the existing focus on cardiac and infectious disease parameters.

FIGURE 5 Long-Term Survival of DUA-IE and Comparison by Surgical Intervention


A
100%
75%
50%
25%
0%
Survival Probability
P = 0.00021
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (Years)
Number at risk
PWID-IE 92 68 57 48 37 34 29 20 15 12 10 9 2
PWID-no-IE 100 91 82 72 60 51 45 40 32 26 18 13 1
B
100%
75%
50%
25%
0%
Survival Probability
P = 0.067
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (Years)
Number at risk
PWID-Not-Operated 47 37 30 28 22 19 18 14 12 9 7 7 1
PWID-Operated 45 31 27 20 15 15 11 6 3 3 3 2 1
Surgery
PWID-Not-Operated
PWID-Operated

(A) Long-term survival is diminished in PWID with IE as compared to PWID with other infections. **(B)** Long-term survival is worse among patients with DUA-IE who had surgical intervention compared to those who did not. Reproduced with permission from Straw et al.[10] Abbreviations as in Figures 1 and 4.

Although retention in treatment with medications for opioid use disorder (MOUD) is associated with a 70% reduction in mortality in the month that MOUD was received, MOUD initiation alone is insufficient treatment because of postdischarge drop-off in treatment retention [41] and the percentage of individuals who start treatment in most existing cohort studies has been <10%.[19] Evidence supports inpatient addiction consultation services as an important resource for the management of patients hospitalized with addiction and associated infections.[37,42] Addiction consultation was associated with increased completion of antibiotics (OR: 5.57; 95% CI: 2.25-13.07; $P < 0.0001$), decreased patient-directed discharges (OR: 0.19; 95% CI: 0.08-0.48; $P < 0.0003$), and increased rates of MOUD adherence (OR: 31.68; 95% CI: 10.25-81.29; $P < 0.001$) among individuals with drug use-associated infections.[32,43] The University of Alabama-Birmingham developed a 9-point scale of clinical and psychosocial risk factors to stratify PWID as low risk (≤3 points), those who were discharged for antibiotic completion duration, and medium or high risk (≥4 points), those who remained hospitalized for treatment completion while receiving group therapy and medications for addiction treatment (Table 4).[44]

APPROACHES TO MINIMIZE TRAUMA AND REDUCE PATIENT-DIRECTED DISCHARGE. Hospitalization can be a challenging experience for PWID, who describe experiencing inadequate pain treatment, fear of inadequate management for withdrawal symptoms, and drug cravings during long hospitalizations, which can lead to high rates of patient-directed discharges (previously "against medical advice"), with complex hospital readmissions often increasing mortality.[45,46] Patient-directed discharges result in incomplete antibiotic therapy and inadequately formulated treatment plans for SUD. Given that PWID commonly report histories of physical and psychological trauma exacerbated by the feeling of confinement in the hospital, it is important for health care providers to aid in the facilitation of positive interactions to improve care.[45,47] When interacting with patients in the hospital, health care providers should consider approaches drawn from principles of trauma-informed care (Table 5).

Incorporating these principles facilitates patient autonomy to make decisions regarding care and may lessen patient-directed discharge, promote patients education, and improve patient understanding of the team's treatment plans. PWID have also often experienced past stigma in the medical care setting, and establishing a trusting relationship with treating providers can be a common barrier to care. Table 6 lists the language that should be avoided to reduce stigmatization of PWID. Providing patients with support and access to connections with social workers, recovery coaches, and physicians with whom they feel they can develop an alliance allows them the space to voice their questions and concerns.

TABLE 2 Modified Duke Criteria

Definite IE
Pathological criteria
Pathologic lesions (active endocarditis on histology of vegetation or intracardiac abscess)
Microorganism on culture or histology of vegetation or intracardiac abscess
Clinical criteria
2 Major clinical criteria, or
1 Major and 3 minor clinical criteria, or
5 Minor clinical criteria
Possible IE
1 Major and 1 minor clinical criteria, or 3 Minor clinical criteria
Rejected
Firm alternative diagnosis, or Resolution of clinical manifestations ≤4 days of antibiotic therapy, or No pathologic evidence of IE on tissue sample after antibiotic therapy for ≤4 days Clinical criteria for definite or possible IE not met
Major Criteria
Positive blood cultures[a]
Endocardial involvement by echocardiography[b]
Minor Criteria
Predisposition[c]
Fever[d]
Vascular phenomena[e]
Microbiologic evidence[f]
Immunologic phenomena[g]

[a]Typical micro-organisms consistent with IE from 2 separate blood cultures: *Viridans streptococci, Streptococcus bovis*, HACEK group, *Staphylococcus aureus*; or community-acquired enterococci in the absence of a primary focus, or micro-organisms consistent with IE from persistently positive blood cultures defined as follows: at least 2 positive cultures of blood samples drawn >12 hours apart or all 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 hour apart), or single positive blood culture for *Coxiella burnetii* or phase I immunoglobulin G antibody titer >1:800. [b]Echocardiogram positive for IE (transesophageal echocardiogram recommended for patients with prosthetic valves, rated at least possible IE by clinical criteria, or complicated IE [paravalvular abscess]; transthoracic echocardiogram as first test in other patients) defined as follows: oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; abscess; or new partial dehiscence of prosthetic valve or new valvular regurgitation (worsening or changing or pre-existing murmur not sufficient). [c]Intravenous drug use or presence of a predisposing heart condition (prosthetic heart valve or a valve lesion associated with significant regurgitation or turbulence of blood flow). [d]Temperature ≥38.0 °C (100.4 °F). [e]Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, or Janeway lesions. [f]Glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor. [g]Positive blood cultures that do not meet major criteria or serologic evidence of active infection with organism consistent with IE.

IE = infective endocarditis.

ETHICAL ASPECTS. For the treating team, ethical predicaments accompany many cases of DUA-IE, balancing the risk of recurrent IE among people who continue to use drugs, while trying to provide equitable health care to PWID. The concept of a treatment agreement or "contract" between a patient and surgeon has been advocated, but concerns exist that this may discourage individuals from seeking health care when needed and, more importantly, undermines the

TABLE 3 Diagnostic Imaging Modalities in DUA-IE

Modality	Advantages	Test Characteristics in NVE		Test Characteristics in PVE		Disadvantages
		Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	
TTE	Availability Noninvasive Repeatable 3D visualization of right-sided structures	65-71	95	~50	91-98	May be limited for full definition of left-heart structures and for complications of endocarditis Lower sensitivity
TEE	Visualization of left-sided structures High temporal resolution 3D is useful in detecting vegetations, diagnosing valve perforation and intracardiac fistula	Overall for leaflet pathology (vegetation): 91-97, perforation: 79-87.5 Perivalvular complications: 44-73	Overall for leaflet pathology (vegetation): 83-88, perforation: 93 Perivalvular complications: 80-100	Overall for leaflet pathology (vegetation, perforation): 82-92 Valve dehiscence: 66.6	Overall for leaflet pathology (vegetation, perforation): 74-90 Valve dehiscence: 99.2	Invasive procedure, may require general anesthesia (higher likelihood of tolerance to conscious sedation if opioid use disorder)
MDCTA	Axial and 3D images of valve structures High spatial resolution Gating with cardiac cycle Assesses for extracardiac lung and chest complications simultaneously (eg, septic pulmonary emboli) Useful in diagnosing perivalvular abscess Ability to assess coronary arteries	Overall 57-85 Perivalvular complications: 88	Overall 58-84 Perivalvular complications: 93-97	Overall 78-93 Valve dehiscence: 45	Overall 83-94 Valve dehiscence: 97	Radiation Nephrotoxic contrast May require lower ambient heart rate Less accurate for small vegetation (<10 mm)
PET/CT	Anatomic-functional correlate for site of infection May be best suited for prosthetic and CIED infections and identifying extracardiac foci of infection (can identify PVE even with negative cultures and echocardiography)	31-76.8	77.9-99	74-81 91 if exclude CRP <40 mg/L and prior use of surgical adhesive	79-91 95 if exclude CRP <40 mg/L and prior use of surgical adhesive	Availability Low accuracy in NVE Radiation Expense Accuracy affected by blood glucose level and diet, ambient inflammation, antimicrobial therapy, use of surgical adhesive (PVE)

Perivalvular complications include paravalvular leak, abscess, pseudoaneurysm, and fistula, and prosthetic dehiscence. Data are from Erba et al,[22] Sifaoui et al,[23] Wang et al,[24] Mahmood et al,[27] Bai et al,[28] Jain et al,[104] Kamani et al,[105] Albano et al,[106] and Swart et al.[107]

3D = 3-dimensional; CIED = cardiac implantable electronic device; DUA-IE = drug use–associated infective endocarditis; MDCTA = multidetector computed tomography angiography; NVE = native valve endocarditis; PET/CT = positron emission tomography/computed tomography; PVE = prosthetic valve endocarditis; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

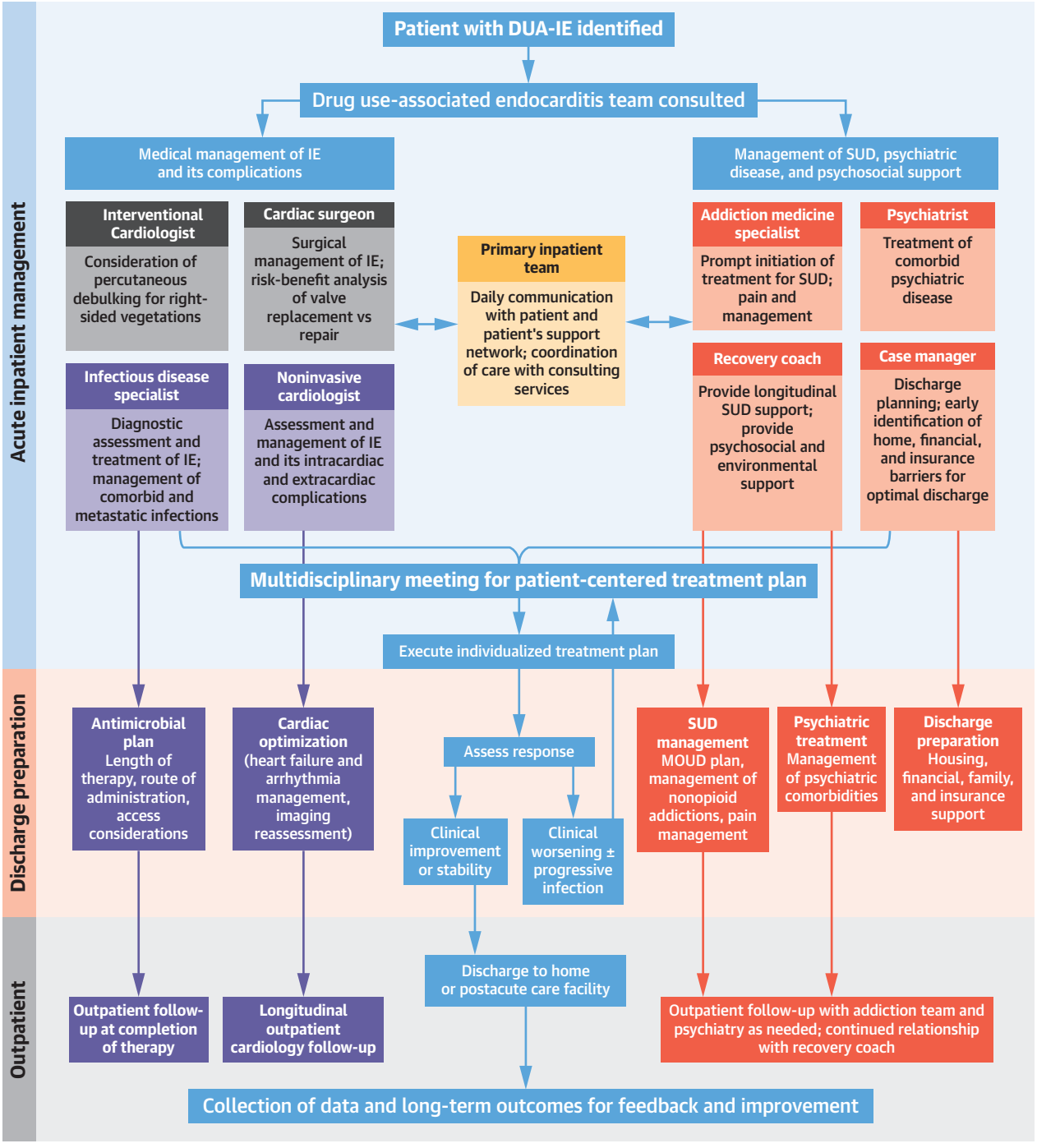
complexity of the underlying disorders that PWID experience.[48,49] Decisions around medical futility vs utility are often challenging, especially in cases of DUA-IE in the presence of multiple reoperations or prior prosthetic valves. Ultimately surgical intervention may be futile without adequate source control, that is, treatment of underlying SUD. In these instances engagement of an ethics committee may be helpful.

TREATMENT OF DUA-IE

ANTIMICROBIAL THERAPY. Clinical practice guidelines from the AHA, endorsed by the Infectious Diseases Society of America, provide detailed guidance for antimicrobial therapy in native and prosthetic valve IE, tailored to microbiologic data.[20] Clinicians should use Gram stain information (which is often available early in the diagnostic evaluation) to guide empiric therapy. If gram-positive organisms are suspected, then empiric coverage often includes antimethicillin resistant *S aureus* antibiotics, such as vancomycin. If gram-negative organisms are suspected, then antibiotics that include coverage of *Pseudomonas* spp, such as cefepime, should be considered because injection practices may involve nonsterile water. Once mature cultures are available, tailored regimens should be used. **Table 7** includes common treatment regimens used for pathogens frequently cultured in native valve DUA-IE.

UNIQUE ISSUES IN ANTIMICROBIALS IN DUA-IE. Whereas standard treatment for IE often involves 6 weeks of antimicrobial therapy, guidelines support the use of abbreviated treatment courses for certain scenarios of right-sided IE, which is more common in DUA-IE.[20] Abbreviated regimens have the benefit of less exposure to antimicrobials and, when relevant, less time with an indwelling catheter in place.

CENTRAL ILLUSTRATION **Multidisciplinary Approach to Caring for Patients With Drug Use–Associated Infective Endocarditis**


Acute inpatient management
Patient with DUA-IE identified
Drug use-associated endocarditis team consulted
Medical management of IE and its complications
Management of SUD, psychiatric disease, and psychosocial support
Interventional Cardiologist
Consideration of percutaneous debulking for right-sided vegetations
Cardiac surgeon
Surgical management of IE; risk-benefit analysis of valve replacement vs repair
Primary inpatient team
Daily communication with patient and patient's support network; coordination of care with consulting services
Addiction medicine specialist
Prompt initiation of treatment for SUD; pain and management
Psychiatrist
Treatment of comorbid psychiatric disease
Infectious disease specialist
Diagnostic assessment and treatment of IE; management of comorbid and metastatic infections
Noninvasive cardiologist
Assessment and management of IE and its intracardiac and extracardiac complications
Recovery coach
Provide longitudinal SUD support; provide psychosocial and environmental support
Case manager
Discharge planning; early identification of home, financial, and insurance barriers for optimal discharge
Multidisciplinary meeting for patient-centered treatment plan
Execute individualized treatment plan
Discharge preparation
Antimicrobial plan
Length of therapy, route of administration, access considerations
Cardiac optimization
(heart failure and arrhythmia management, imaging reassessment)
Assess response
Clinical improvement or stability
Clinical worsening ± progressive infection
SUD management
MOUD plan, management of nonopioid addictions, pain management
Psychiatric treatment
Management of psychiatric comorbidities
Discharge preparation
Housing, financial, family, and insurance support
Outpatient
Discharge to home or postacute care facility
Outpatient follow-up at completion of therapy
Longitudinal outpatient cardiology follow-up
Outpatient follow-up with addiction team and psychiatry as needed; continued relationship with recovery coach
Collection of data and long-term outcomes for feedback and improvement

Yucel E, et al. J Am Coll Cardiol. 2022;79(20):2037–2057.

Proposed care pathway and multidisciplinary involvement for a patient admitted with drug use–associated infective endocarditis (DUA-IE). IE = infective endocarditis; MOUD = medications for opioid use disorder; SUD = substance use disorder.

TABLE 4 9-Point Risk Assessment for PWID

Risk Factor (1 Point Each)
1. Cravings
2. Unstable home environment
3. Dual psychiatric diagnosis
4. History of drug overdose
5. History of multiple relapses
6. Polysubstance abuse
7. Family history of addiction
8. History of trauma
9. Limited willingness to change

Adapted with permission from Eaton et al.[44]
PWID = persons who inject drugs.

Medication interactions are another important consideration, because there are multiple potential interactions between common antimicrobial agents with MOUD or psychiatric medications. Rifampin, used in the context of *S aureus* prosthetic valve endocarditis, is a potent CYP3A4 inducer; concurrent use of rifampin with either buprenorphine or methadone may lead to reduced levels of these MOUD agents, thus requiring higher doses.[50,51] Linezolid, used in the setting of vancomycin-resistant *Enterococcus* spp IE, is a monoamine oxidase inhibitor and may result in increased risk of serotonin syndrome in the setting of opioids.[51] QTc prolongation may be caused by fluoroquinolone and azoles, and in combination with methadone, several classes of antidepressants, and antipsychotics, which may be used for concurrent psychiatric illnesses.[51]

While there are some perceived risks of discharging a PWID with an indwelling line to a home setting, several recent studies have demonstrated that PWID can successfully complete outpatient parenteral antimicrobial therapy in routine ambulatory settings.[52,53] Additionally, the rising frequency of patient-directed discharges in patients with DUA-IE raises the issue of alternative therapy options for patients who wish to leave the hospital prior to having a treatment plan in place. One approach to this challenging situation includes convening a structured interprofessional planning meeting, including case managers and outpatient pharmacists, to discuss discharge planning options while focusing on harm reduction and patient-centered considerations.[54]

TABLE 5 Principles of Trauma-Informed Care

Focus on creating a welcoming and safe environment for patients, acknowledging that health care settings can be a challenging place for patients with a history of trauma.
Always use person-first language and avoid stigmatizing ways of describing substance use or people who use substances (see Table 6 for language to be avoided).
Attempt to have consistent health care providers and to limit the number of providers in the room at one time.
When introducing yourself, be sure to clearly identify who you are and what your role is on the team.
When possible, do not stand over patients, rather sit with them meeting them at eye level.
Ask permission to touch the patient and move the patient's belongings if necessary.
Elicit patient's subjective needs and, when possible, try to meet these needs.
When possible, allow the patient opportunities to express their goals, preferences, and agency regarding treatment options.
Let the patient know that you are there to collaborate in the development of a successful treatment plan, working with them toward a solution or goal.

Oral antibiotics may be the agent of choice in certain circumstances, but more commonly gold-standard therapy includes parenteral antimicrobials for DUA-IE. A large, randomized trial found that early switch from parenteral to oral antibiotics for left-sided endocarditis is noninferior.[55] However, it should be noted that it is hard to generalize results to the DUA-IE because only 5 of 400 PWID were randomized. Additionally, less than one-quarter had *S aureus*, and importantly, there were neither cases of methicillin-resistant *S aureus* nor other "antibiotic-resistant phenotypes."

While long-acting lipoglycopeptide antibiotics with activity against *S aureus*, including dalbavancin, telavancin, and oritavancin, are promising, at present there are both regulatory and logistic challenges to using these agents for the treatment of IE. Though there are retrospective reports of successfully treated cardiovascular infections with these agents,[56,57] they are not approved by the U.S. Food and Drug Administration (FDA) for treatment of bacteremia or IE. Cost, insurance approval, and access to an infusion site may pose significant barriers to their use that warrant further exploration.

SURGICAL THERAPY. Cardiac surgery for IE may be technically complex because of extensive tissue destruction, and whereas perioperative mortality may be less, long-term outcomes are worse when compared with those of surgery for noninfectious etiologies.[58,59] Among patients undergoing surgery for IE, both overall incidence as well as the proportion of patients with DUA- IE with or without prior valve surgery are increasing.[9,60] Recent meta-analysis showed PWID had 47% greater hazard of death and more than twice the hazard of reoperation than non-PWID did, with 40% mortality 5 years after surgery;[61] although, results from 1 large single-center surgical study indicated similar 5-year survival and operative mortality among patients with and those without DUA-IE.[62] Others have identified active endocarditis, emergency intervention, dialysis, liver disease, enterococcal infections, lung disease, prosthetic valve endocarditis, aortic valve disease, and multivalve disease as predictors of increased short-term mortality after surgery for DUA-IE,[63,64] leading

to the creation of the STOP (Stratification Risk Analysis in Operative Management) score to predict operative morbidity and mortality in DUA-IE (Table 8).[63]

Although DUA-IE is an increasingly prevalent and devastating problem, current valvular heart disease guidelines from the American College of Cardiology and AHA provide only limited guidance on surgical treatment of endocarditis for PWID.[65] The 2015 AHA endocarditis guidelines suggest avoiding surgery given subsequent risk of prosthetic infection from drug use.[20] Because right-sided DUA-IE has been more common, this is the focus of these 2015 surgical guidelines,[20] which support surgery largely in parallel to the 2015 ESC guidelines for failed medical therapy, septic pulmonary embolism, and large vegetations, especially if there is a patent foramen ovale present with right-to-left shunting, which can increase the risk of paradoxical systemic emboli (Table 9). Tricuspid regurgitation is generally well tolerated even when it is severe and is less commonly an indication for surgery unless the patient experiences right-sided heart failure with poor response to diuretics. The availability of percutaneous mechanical aspiration (PMA) techniques provides an additional tool for treating right-sided endocarditis.

When feasible, valve repair is preferable to valve replacement[65] and is associated with lower risk of reinfection.[66] Because most patients with DUA-IE are young, mechanical valves would typically be recommended according to the American College of Cardiology/AHA guidelines;[65] however, prosthesis choice for PWID is complicated by the additional challenge of compliance with an anticoagulation regimen in the setting of the adverse social and health care circumstances of many such patients. A study by Toyoda et al,[67] which compared long-term outcomes (12-year follow-up with a median of 6.8 years) in patients undergoing valve replacement using bioprosthetic or mechanical valves for IE, demonstrated that drug use was an independent predictor of worse 12-year survival, increased recurrence, and increased risk of reoperation, but that among PWID, there was no significant difference in long-term outcomes and susceptibility to recurrent infection between prostheses. In practice, bioprosthetic valves are frequently implanted for patients with DUA-IE despite their young age.[68]

Cryopreserved allografts (homografts) have been used infrequently for active IE during primary operations (7.0%) but were more common (32.2%) in the setting of reoperation for prosthetic valve endocarditis.[68] Some investigators argue in favor of allografts as the preferred conduit for patients with extensive aortic root infection, especially in the setting of prosthetic valve endocarditis, because allografts are thought to be more resistant to reinfection.[26,69] They may also provide some technical advantages, such as the availability of the anterior mitral leaflet for recreation of aortomitral continuity, and superior pliability as compared to xenograft prosthetic valves; however, their use is restricted by limited availability and lack of surgeon familiarity. Additionally, data regarding the superiority of allografts in endocarditis are conflicting, and several studies have shown equivalent outcomes in mortality and reinfection rates among prosthetic valve conduits in endocarditis.[70-72] Recently, a new technique of aortic valve reconstruction using autologous pericardium was described by Ozaki et al.[73] It has been proposed that this approach may provide superior resistance to infection as no foreign material is used,[74] although this hypothesis remains to be proven clinically.

For those with recurrent endocarditis and continued injection drug use, consultation with experts in addiction medicine regarding long-term

TABLE 6 Language to Avoid to Reduce Stigmatization of PWID

	Use	Avoid
Talking about yourself or others with SUD	Person with a substance use disorder Person with an opioid use disorder or person with opioid addiction	Addict User Substance or drug abuser Junkie
	Person with alcohol use disorder Person who misuses alcohol/engages in hazardous alcohol use	Alcoholic Drunk
	Person in recovery or long-term recovery Person who previously used drugs	Former addict Reformed addict
	Testing positive (on a drug screen)	Dirty Failing a drug test
Talking about using substances	Substance use disorder Drug addiction	Habit
	Use (for illicit drugs) Misuse (for prescription medications used other than prescribed)	Abuse
Talking about recovery and treatment	Medication treatment for opioid use disorder Medications for opioid use disorder Opioid agonist therapy Pharmacotherapy Medication for a substance use disorder	Opioid substitution Replacement therapy Medication-assisted treatment
	Being in remission or recovery Abstinent from drugs Not drinking or taking drugs Testing negative (on a drug screen)	Clean
Talking abouts babies born to parents who use drugs	Baby born to a parent who used drugs while pregnant Baby with signs of withdrawal from prenatal drug exposure Newborn exposed to substances Baby with neonatal abstinence syndrome	Addicted baby

Adapted with permission from National Institute on Drug Abuse recommendations.[108]
PWID = persons who inject drugs; SUD = substance use disorder.

TABLE 7 Antimicrobial Regimens for Common DUA-IE Pathogens in NVE

Pathogen	Antimicrobial	Dose[a]	Duration
Methicillin-susceptible *Staphylococcus aureus*	Nafcillin or oxacillin	12 g per 24 h divided in 4-6 doses, intravenously	4-6 weeks[b]
	Cefazolin	6 g per 24 h divided in 3 doses, intravenously	
Methicillin-resistant *Staphylococcus aureus*	Vancomycin	30 mg/kg per 24 h divided in 2-3 doses, intravenously[c]	6 weeks
Viridans group streptococci	Ceftriaxone	2 g per 24 h, intravenously or intramuscularly	4 weeks
	Aqueous crystalline penicillin G sodium[d]	12-18 million units per 24 h divided in 4-6 doses, intravenously	4 weeks

Consultation by infectious disease specialists for antimicrobial management is strongly recommended. Adapted with permission from American Heart Association infective endocarditis guidelines.[20] [a]Assumes normal renal function. [b]A 4-week course of therapy may be considered for uncomplicated right-sided MSSA IE. [c]Consider loading dose, and therapeutic drug level monitoring is recommended. [d]For highly penicillin-susceptible viridans group streptococci species (MIC ≤0.12 μg/mL).

MIC = minimum inhibitory concentration; MSSA = methicillin-sensitive *Staphylococcus aureus*; other abbreviations as in Tables 1 and 3.

ability to refrain from drug use is recommended (Class I) as a component of decision making regarding reoperation.[65] Opinions vary widely even within a single institution regarding the ethics and utility of reoperative cardiac surgery in the setting of prosthetic valve endocarditis and recurrent or ongoing injection drug use.[75,76] Because of this, a multidisciplinary team approach may help address bias and facilitate providing individualized care that is equitable across populations. Although there are no absolute contraindications for surgery, engagement around treatment planning, which includes treatment of SUD, is an important factor in consideration for surgical intervention in PWID.

PMA OF VEGETATIONS. In recent years, PMA has been evaluated for debulking right-sided vegetations and has been proposed as an alternative to surgery with goals of reducing bacterial load and inoculum size, facilitating antimicrobial treatment, decreasing risk of embolization, and providing time to address root causes of infection and SUD.[77-79] PMA is performed using a continuous suctioning circuit that allows aspiration of lesions of interest, filtration of blood/aspirate mix, and reinfusion of filtered blood back to the patient. General anesthesia is typically required for the procedure because its veno-venous extracorporeal bypass requires large-bore access. Preprocedural transesophageal echocardiogram should obtain baseline imaging evaluating the extent of vegetations, severity of tricuspid regurgitation, and presence of interatrial shunt, which may increase the possibility of paradoxical embolism and alter the suitability of extraction (Figure 6). Intraprocedural transesophageal echocardiogram guidance allows direct visualization of lesions of interest and monitoring for complications, including valvular injury and disruption of the pericardial space.

Data regarding PMA suggest a favorable safety profile. George et al[77] reported a single-center review of 33 patients, 24 of which were PWID, with tricuspid valve IE treated with PMA of vegetations. Vegetation size decreased from a preprocedural average of 21 ± 7 mm to 8 ± 5 mm postprocedurally. One patient experienced cardiac tamponade directly related to the procedure. Although the average severity of tricuspid regurgitation increased after vegetation PMA, all patients survived the procedure, and 30 of 33 patients survived the index hospitalization. One-third of patients required blood transfusion with an average of 2.7 units of packed red blood cells. Moriarty et al[78] reported results from a prospective multicenter registry of 234 PMA procedures, 59 of which were for right-sided vegetation debulking. Most patients with right heart vegetations had >50% of materials removed. There were 3 deaths (1.3%), with 1 procedure-related death caused by distal embolism of inferior vena cava thrombus leading to a massive pulmonary embolism. Pericardial effusion developed in 2 patients (0.8%), 1 of which required pericardial drainage. Caval rupture or extravasation occurred in 2 patients (0.8%) and was treated percutaneously with angioplasty and stent deployment. Twenty-five percent of patients required blood transfusion with an average of 1.9 units of packed red blood cells.

There are several limitations to PMA of vegetations. Residual vegetation is commonly present at the end of the procedure, and PMA does not address valvular abscesses or leaflet destruction. Accordingly, PMA may be futile, and multidisciplinary discussion regarding its use is essential. Additionally, the system is only designed to be used in right-sided lesions, although there is some experience addressing left heart vegetation via transeptal access.

As less invasive alternatives to traditional surgery such as PMA become more readily available, the threshold to initiate discussion of invasive treatments may be revisited. For example, ESC guidelines recommend surgery for vegetations >20 mm in size for right-sided IE in the presence of pulmonary embolism with or without right-sided heart failure.[26] It is unclear whether applying a smaller threshold to trigger percutaneous debulking may be beneficial. It is also conceivable that repetitive percutaneous debulking of vegetations finds a particular niche in patients with an increased risk of recurrence. Also, there are possibly fewer procedure-related infectious

complications with percutaneous debulking compared with sternotomy. Last, the less invasive nature of PMA compared with surgery may translate to reduced analgesia requirements in the post-procedure recovery phase. As global experience is just emerging and the benefit of PMA remains to be proven in clinical trials, there are currently insufficient data to integrate PMA in routine clinical practice.

TREATMENT OF ADDICTION

GENERAL CONCEPTS. Individuals hospitalized with serious infectious complications of SUD should be offered consultation with an addiction medicine- or addiction psychiatry-trained physician or advanced practice practitioner. Addiction consultation teams are critical in providing patient-centered care, support, and ensuring adequate symptom management, particularly during prolonged hospitalizations, but such teams are unfortunately not available in all hospitals.[35,37,42] With increasing hospitalizations among PWID, there is a growing need for trained providers to be able to manage SUD. Hospitalization can offer a "reachable moment" and initiating addiction treatment during the hospital admission improves postdischarge outcomes including reducing addiction severity and improving engagement in ongoing SUD care.[37]

TABLE 8 STOP Score

	Score for Operative Morbidity[a]	Score for Operative Mortality[a]
Dialysis	3	5
No dialysis	0	0
Emergent status	5	6
Nonemergent status	0	0
Multivalve procedure	2	3
Single-valve procedure	0	0
Organism other than *Streptococcus*	2	–
Streptococcus	0	–
Aortic valve procedure	2	5
Nonaortic valve procedure	0	0
Mitral valve procedure	2	–
Nonmitral valve procedure	0	–
Tricuspid valve replacement	3	–
Tricuspid valve repair	0	–
Active or treatment resistant endocarditis	–	5
Treated endocarditis	–	0
Lung disease at baseline	–	5
No lung disease at baseline	–	0
Prosthetic valve endocarditis	–	4
Native valve endocarditis only	–	0
Total possible points	19[b]	33[c]

Adapted with permission from Habertheuer et al.[63] [a]Each point increased odds of morbidity and mortality by 22.0% and 22.4% with an accuracy of 94.0% and 94.1%, respectively. [b]Predicted operative morbidity ranged from 19.7% (0 STOP points) to 84.9% (16 STOP points). [c]Predicted operative mortality ranged from 0.5% (0 STOP points) to 56.2% (27 STOP points).

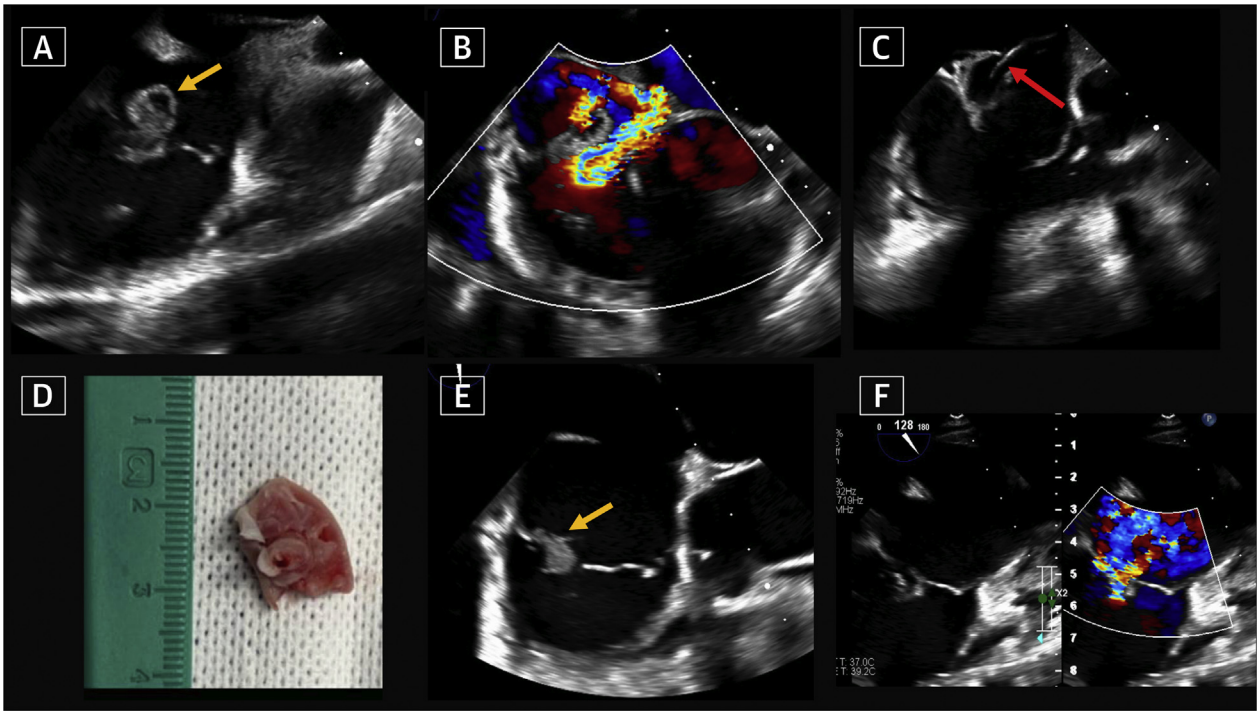
STOP = Stratification Risk Analysis in Operative Management.

APPROPRIATE MEDICAL MANAGEMENT OF SUD. SUD is highly treatable, and if provided appropriate resources and support most people will achieve remission, meaning they will no longer meet criteria for active SUD. For example, SUD treatment follow-up studies have generally demonstrated that 40%-60% of patients who are discharged are continuously abstinent and an additional 15%-30% have not resumed problematic, heavy substance use in the first year following treatment.[80] As with other chronic medical conditions, treatment generally involves some combination of counseling, medication, and ongoing monitoring. Among SUD, there are approved pharmacologic treatments for alcohol, tobacco, and opioid use disorder. Because of the efficacy of pharmacologic treatments, remission rates from opioid use disorder treated with medication are particularly favorable.[81]

Table 10 lists all the FDA-approved MOUDs. First-line MOUD include methadone and buprenorphine and the second-line medication is extended-release naltrexone. MOUD improves retention in treatment and remission while reducing ongoing opioid use and other adverse outcomes more than psychosocial or other treatments do.[82] Methadone and buprenorphine reduce all-cause mortality and overdose-related mortality compared to psychosocial or no treatment, with observed mortality reductions of up to 50%.[82,83] Extended-release naltrexone is more effective than placebo or counseling alone, but it is associated with lower rates of treatment retention and abstinence from nonprescribed opioids as compared to buprenorphine.[84,85] Psychosocial-only treatments have been shown repeatedly to be inferior to MOUD, and randomized clinical trials studying the benefit of adjunctive cognitive behavioral therapy, contingency management (giving positive incentives for treatment engagement or abstinence), or individual counseling have not demonstrated improved outcomes compared to medical management alone with MOUD.[86,87] Based on available evidence, all patients with opioid use disorder should be offered no-barrier access to medication; although individualized psychosocial treatment should be made available, it should not be required for patients treated with MOUD.

In contrast to established options for MOUD, the mainstay of treatment for stimulant use disorder, including methamphetamine and cocaine, continues to be psychosocial treatments because there is a lack

FIGURE 6 TEE Images From a Patient Who Underwent PMA



(A) Transesophageal echocardiogram (TEE) modified right ventricular (RV) inflow view of the tricuspid valve (TV) showing a large mobile vegetation **(yellow arrow)** on the atrial side of the anterior leaflet of the TV in a patient with drug use–associated infective endocarditis. **(B)** Color Doppler shows severe tricuspid regurgitation. **(C)** Modified RV inflow view during percutaneous mechanical aspiration (PMA) of the TV vegetation. **Red arrow** points to the suction catheter. **(D)** Pathological sample of the vegetation that was aspirated during PMA. *Staphylococcus aureus* was cultured from the pathological specimen. **(E)** Modified RV inflow-outflow view of the TV on immediate postprocedural TEE showing residual vegetation on TV despite multiple attempts of aspiration. **(F)** Color Doppler still shows severe tricuspid regurgitation.

of FDA-approved pharmacotherapy. A 2020 systematic review[88] evaluated 11 interventions for stimulant use disorder including contingency management, cognitive behavioral therapy, acupuncture, antidepressants, dopamine agonists, antipsychotics, anticonvulsants, disulfiram, opioid agonists, N-acetylcysteine, and psychostimulants and found that only contingency management programs were supported by sufficient evidence. Though limited, other reviews[89,90] specifically examining different pharmacotherapies have shown low-strength evidence to support methylphenidate for reducing ongoing methamphetamine use and bupropion, topiramate, and psychostimulants to improve cocaine abstinence. Additionally, a 2021 multisite, double-blind, placebo-controlled trial[91] evaluating the efficacy of extended-release naltrexone plus oral bupropion for methamphetamine use disorder found that this medication combination resulted in a higher treatment response, defined as at least 75% methamphetamine-negative urine samples. Given the morbidity associated with ongoing stimulant use disorder, particularly in individuals with DUA-IE, a trial of bupropion, topiramate, bupropion plus naltrexone, or psychostimulants may be reasonable, in addition to incorporating contingency management programs. Additional studies in this area are required to better define potential benefits associated with these treatments. An increasing challenge is rising prevalence of co-occurring stimulant use among people with opioid use disorder, particularly methamphetamine use.[92] For patients with co-occurring opioid use disorder and stimulant use disorder, studies have demonstrated that the use of MOUD is significantly lower.[92] Providing contingency management and cognitive behavioral therapy to patients being treated with MOUD who have co-occurring SUD has been shown to reduce stimulant use. Based on these findings, it is recommended that patients with co-occurring opioid use disorder and SUD be offered no-barrier access to MOUD and concurrent treatment for their stimulant use disorder.

TABLE 9 ACC/AHA and ESC Indications for Surgical Intervention in Endocarditis

AHA Endocarditis Guidelines (2015)[20] ACC/AHA Valvular Heart Disease Management Guidelines (2021)[65]	ESC Endocarditis Guidelines (2015)[26]
Valve dysfunction causing HF (Class I)	Aortic or mitral NVE or PVE with severe acute regurgitation, obstruction or fistula causing refractory HF or cardiogenic shock or echocardiographic signs of poor hemodynamic tolerance (Class I)
Complications of heart block, annular or aortic abscess, or penetrating lesions (fistulas) (Class I)	Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation) (Class I)
IE caused by *Staphylococcus aureus*, fungal, or highly resistant organisms (Class I)	Infection cause by fungi or multiresistant organism (Class I)
Persistent infection evidenced by bacteremia or fevers >5 d on antibiotic treatment (Class I)	Persistent positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci (Class IIa)
Prosthetic valve endocarditis with relapsing infection (Class I)	PVE caused by staphylococci or non-HACEK gram-negative bacteria (Class IIa)
Recurrent emboli or persistent vegetations despite antibiotic treatment (Class I)	Aortic or mitral NVE or PVE with persistent vegetations >10 mm after ≥1 embolic episodes despite appropriate antibiotic therapy (Class I)
Large (>10 mm) mobile vegetations (Class IIb)	Aortic or mitral NVE with vegetations >10 mm, associated with severe valve dysfunction and low operative risk (Class IIa)
	Aortic or mitral NVE or PVE with isolated very large vegetations (>30 mm) (Class IIa)
	Aortic or mitral NVE or PVE with isolated large vegetations (>15 mm) and no other indication for surgery (Class IIa)
DUA-IE–Specific Right-Sided Endocarditis Guidelines	
It is reasonable to avoid surgery when possible in patients who are injection drug users (Class IIa)	Right heart failure caused by severe tricuspid regurgitation refractory to diuretics
Surgical intervention reasonable for patients with right heart failure secondary to severe tricuspid regurgitation with poor response to medical therapy	IE caused by organisms that are difficult to eradicate or bacteremia for ≥7 d (eg, *S aureus, Pseudomonas aeruginosa*) despite adequate antimicrobial therapy
Surgical intervention reasonable for patients with sustained infection caused by difficult-to-treat organisms (ie, fungi, multidrug-resistant bacteria) or lack of response to appropriate antimicrobial therapy	Tricuspid valve vegetations >20 mm that persist after recurrent pulmonary emboli with or without concomitant right HF
Surgical intervention reasonable for patients with tricuspid valve vegetations that are ≥20 mm in diameter and recurrent pulmonary embolism despite antimicrobial therapy	
Valve repair rather than replacement should be performed when feasible	

Adapted with permission from Baddour et al,[20] Sifaoui et al,[26] and Kilic et al.[65]

ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; HF = heart failure; other abbreviations as in Tables 1 and 3.

DISCHARGE PLANNING AND COUNSELING. As a patient's clinical status improves, the hospital care team will begin the process of identifying safe and appropriate discharge locations (Central Illustration). Discharge planning should consider the expressed preferences of the patient; some patients may have financial or geographic constraints that should be accommodated whenever possible. Considerations to allow for continuation of antibiotic treatment for endocarditis and medication treatment for SUD are paramount. Notably, many postacute care facilities are not prepared to treat patients with MOUD or other medications for addiction treatment without support.[93,94] Methadone, in particular, can be challenging to administer to patients in postacute care settings, because there are federal laws limiting the use of methadone for the treatment of addiction to opioid treatment programs.[95] Case managers may need to refer patients to more postacute care facilities than usual or may need to inquire specifically about a facility's ability to continue MOUD. Importantly, patients and postacute care facilities should be regularly reminded that individuals engaged in treatment for addiction are protected from discrimination under the Americans with Disabilities Act, and individuals experiencing discriminatory behaviors should be encouraged to report them through the appropriate channels. Discharge counseling with patients should be done using a harm reduction framework, acknowledging explicitly that addiction can be a recurring and remitting chronic condition, and that when abstinence is not possible, individuals can always protect themselves by using substances in a safer way and by carrying the overdose reversal agent naloxone.

HARM REDUCTION, PREVENTION, AND SCREENING. A critical component of all SUD treatments including those with DUA-IE is the incorporation of harm reduction. Harm reduction is a nonjudgmental, noncoercive, person-centered approach to care that respects the dignity and autonomy of people who use drugs and focuses on reducing negative consequences of drug use, such as infectious complications and overdose, and improving individuals' health and quality of life. Harm reduction recognizes that some people will continue to use drugs and therefore

TABLE 10 FDA-Approved MOUD

Medication	Mechanism at mu-Opioid Receptor	Route(s) of Administration	Dosing Frequency
First-line			
Methadone	Full agonist	Pill, liquid, wafer	Daily
Buprenorphine	Partial agonist	Pill, film Extended-release injectable	Daily Injectable is every 4 weeks
Second-line			
Naltrexone	Antagonist	Oral, extended-release injectable	Daily or monthly (for injectable)

FDA = U.S. Food and Drug Administration; MOUD = medications for opioid use disorder.

minimizing associated risk is an important health priority, particularly for persons with DUA-IE where subsequent infection is driven not necessarily by drug use per se, but rather by use practices and access to sterile injection equipment. Harm reduction interventions, include syringe service programs, have been shown to increase engagement and access to care and to reduce infectious complications and overdose.[96] In addition to managing the acute infection of DUA-IE, prevention of recurrent bacteremia and subsequent IE should be attempted. Although this includes treatment of the underlying SUD, along with providing dental prophylaxis after an episode of IE per AHA guidelines, counseling regarding safe injection practices and providing access to sterile injection equipment has also been shown to reduce the risk for invasive bacterial infections.[97,98] Last, other infections that might be acquired via injection drug use, including HIV and hepatitis B and C, should be screened for and treated as indicated. Patients should be vaccinated against infections that can be contracted via injection practices including tetanus and hepatitis B or those that are specifically recommended for PWID, such as hepatitis A.[99] Offering preexposure prophylaxis has been approved by the U.S. Food and Drug Administration for patients at high risk of HIV acquisition, including PWID who share injection equipment, and should be considered.[100] Additionally, the U.S. Department of Health and Human Services and the Centers for Disease Control and Prevention recommend postexposure prophylaxis for PWID who have a high risk of exposure (ie, sharing equipment with someone who is known to be HIV infected).[101]

CONCLUSIONS

Persons with DUA-IE represent a unique challenge to the medical community and multidisciplinary approach is necessary for optimal outcomes (**Central Illustration**). The prevalence of DUA-IE has increased dramatically over the past decade, and defining and disseminating optimal treatment approaches and best practices represents an urgent clinical and moral imperative. Given the lack of clinical research that has been inclusive of PWID, there are unfortunately very limited prospective observational or experimental data to guide treatment of DUA-IE. Collaborating with experts in addiction and bioethics to aid in the designing studies that are informative and ethical may be helpful in investigating medications and treatment options. Data limitations in this area leave clinicians in the realm of expert opinion and highlight the importance of a multidisciplinary approach to the care of this complex and vulnerable patient population. More broadly, evidence supports the need for a holistic attitude toward longitudinal care of PWID that integrates expertise across professions and specialties. In highlighting the scope of this problem and potential benefits of this approach, we urge societal guidance on specific tailoring of multidisciplinary teams and on the establishment of rigorous prospective research to demonstrate the impact on clinical outcomes. Recognizing that successful treatment of SUD and incorporation of harm reduction are necessary to improve long-term prognosis of patients with DUA-IE, we stress that the cardiovascular team will only be successful in treatment of this patient population by working closely with other care providers and incorporating a focus on addiction treatment and providing appropriate social, psychological, and financial support to patients starting as early as possible.

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